REMARKS

Status Summary

Claims 1-49 are pending upon entry of the request for continued examination. Claims 3, 10-13, 15-23, 30-33, 38-40 and 42-44 are withdrawn from consideration as directed to non-elected invention. Claims 1, 2, 4-9, 14, 24-29, 34-37, 41 and 45-59 were examined. Claims

The examiner is again respectfully thanked for the previous personal interview. During that interview the examiner acknowledged that the then-cited prior art did not teach or suggest antibody dimers comprised of two different intact antibody molecules, each having retained and different antigen-binding properties. A preliminary amendment was filed based on this understanding. A rejection followed after that preliminary amendment which is addressed herein. It is believed that rejections were made because the examiner was of the opinion that applicants' claims did not clearly define the invention, in particular that antibody dimers produced by the subject method comprise two different intact antibodies. It is anticipated that this ambiguity is cured by the present amendments.

Non-elected claims 3, 10-13, 15-23, 30-33, 38-40 and 42-44 are canceled. Claims 37 and 49 are also canceled. Claims 1, 24, 28, 41 and 45 are amended as indicated above.

Objection to the Oath

The objection to the oath is again noted. Office Action, page 2, item 7. A new oath will be provided shortly.

First Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claims 45 and 46 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to specify that the location of the introduced cysteine residue does not adversely affect the ability of antibody to bind antigen after dimerization. Office Action, page 4, item 12. This rejection is traversed.

Claim 45 is amended herein to recite introduction of a cysteine at a location "which does not interfere with the antigen binding properties of said heterodimer." Claim 46 depends from claim 45 and thus also includes this limitation. Thus, applicants respectfully request that the rejection of claims 45-46 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Second Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claim 35 stands rejected under 35 U.S.C. § 112, first paragraph as allegedly requiring the availability of deposited materials (hybridomas) that express specific antibodies. Office Action, page 4, item 13. This rejection is respectfully traversed on the basis that the cited patents, incorporated by reference herein, *i.e.*, U.S. Patent 5,830,698 and 6,011,138 provide the complete DNA and amino acid sequences for the C2B8 (RITUXAN®) and p5E8 antibodies. The amino acid sequence of RITUXAN® is disclosed in U.S. Patent No. 5,736,137, which issued on April 7, 1998. Cells expressing the RITUXAN® antibody are also publicly available from the American Tissue Type Collection as deposit number 69119. U.S. Patent No. 6,011,138 was granted with claims to the p5E8 antibody and did not require deposit of the claimed antibody because its sequence was fully disclosed. Thus, the C2B8 and p5E8 are available to the public either by procurement of deposited cells expressing the C2B8 antibody or by recombinant synthesis using routine techniques. Applicants note that the examiner's rejection is inconsistent with the presumption of claim in accordance with 35 U.S.C. § 282. Based on the foregoing arguments, applicants respectfully request withdrawal of the rejection of claim 35 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims Under 35 U.S.C. § 103(a)

Claims 37, 45 and 46 stand rejected under 35 U.S.C. §103 based on Caron et al. (1992) *J Exp Med* 176:1191-1195 (Caron), in view of Fanger et al. (1992) *Crit Rev Immunol* 12:101-124 (Fanger), Cumber et al. (1992) *J Immunol* 149:120-126 (Cumber), U.S. Patent No. 6,011,138 to Reff et al. (Reff[a]), and Reff et al. (1994) *Blood* 83:435-445 (Reff[b]). The examiner states that the rejection is maintained because "[t]he rejected claims only require a dimeric antibody with two specificities or a heterodimeric antibody." Office Action, page 5, item 14. Applicants respectfully traverse this rejection based on the arguments set forth below.

Claims 1-2, 4-9, 14, 24-29, 34-37, 41, and 47-49 are newly rejected under 35 U.S.C. § 103(a) based on the above-noted references and further in view of the 1994-95 Pierce Catalog (pages T-157, T-163-169). Office Action, page 10, item 17. The Examiner relies on the Pierce Catalog for the teaching heterobifunctional crosslinkers, which include amine and sulfhydryl-reactive groups for conjugation with specific groups to minimize undesirable

claimed invention was made to have produced a method for producing a heterodimeric antibody molecule comprising two different antibodies which bind two antigens." Office Action, page 11, ¶ 6. Applicants respectfully traverse this rejection based on the arguments set forth below.

The examiner bears the burden of presenting a *prima facie* case for obviousness, with a showing of such *prima facie* obviousness requiring: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) the teaching or suggestion of all the claim limitations of the applicant's invention in the combined prior art references; and (3) a reasonable expectation of success. MPEP § 2143. Applicants respectfully submit that the examiner has not met this burden.

With respect to the standing rejection of claims 45 and 46, applicants note that claim 45 is amended herein to clarify that a dimeric antibody produced by the claimed methods is a heterodimer comprising two IgG molecules, wherein each of the two IgG molecules has a unique binding specificity. Based thereon, withdrawal of the rejection of claims 45 and 46 is respectfully requested.

With respect to the new rejection of claims under § 103(a), applicants traverse the rejection on the basis that none of the prior art, by the examiner's own admission, teaches or suggests an antibody heterodimer as claimed. In contrast to the present invention, Caron teaches preparation of an IgG homodimer, wherein the dimerization method does not include the addition of a thiol reactive moiety. The disclosure of Fanger is not directed to antibody dimers, but rather relates to bi-specific antibodies. Cumber similarly pertains to bi-specific antibodies produced by use of chemical cross-linkers. The Reff references are cited based on their disclosure of the specific anti-CD20 and anti-CD23 antibodies used to produced antibody dimers exemplified in this application. The Pierce Catalog is cited based on its disclosure of various hetrobifunctional cross-linkers.

The examiner finds motivation to prepare heterodimeric antibodies in statements by Caron that "multimeric constructs of IgG *may* have advantages relative to those forms that are found naturally" and "several lines of evidence suggest that the proximity of Fc regions of multimeric IgG may explain its enhanced effectiveness." Office Action, page 12.

Applicants respond that the examiner's rejection improperly [illegible]

903, 7 U.S.P.Q.2d 1673, 1680 (Fed. Cir. 1988). The end result of a pursuit is not obvious simply because it may be obvious to try to achieve such a result. In the instant case, the prior art cited is not at all clear whether antibody dimers can be produced that possess advantageous properties, or that antibody multimers even possess enhanced effectiveness. Without this being clear, motivation to prepare antibody heterodimers is not found. The burden of presenting a *prima facie* case for obviousness is not met because the examiner has failed to present any evidence in the art to support his contention that a skilled artisan was, at the time of the instant invention, motivated to prepare a heterodimer as now claimed.

The rejection is further traversed on the basis that it could not have been anticipated that antibody dimers could be obtained that bind two different antigens, *i.e.* which retain the antigen binding properties of two intact antibody molecules. While it is acknowledged that the prior art, suggest that effective bi-specific antibodies can be obtained, the prior art does not anticipate functional bi-specific antibody dimers containing two intact antibody molecules. This outcome, *i.e.*, that the subject antibody dimers bind two different antigens, was not reasonably anticipated, particularly when one considers the large size of antibody molecules, and that steric hindrances reasonably could have resulted in one or both antibodies not retaining antigen binding properties. The fact that antibody multimers exist naturally also does not suggest this outcome as these multimers do not comprise two different antibodies, which are genetically and/or chemically modified to permit dimerization. Rather, such multimers are produced by spontaneous association of antibody molecules *in vivo*.

Based on the foregoing arguments, claims 1-2, 4-9, 14, 24-29, 34-36, 41, and 47-49 are believed to be patentable in accordance with 35 U.S.C. § 103(a). Claim 37 is cancelled, and thus this rejection is rendered moot. Applicants respectfully request withdrawal of the rejection of claims under § 103(a).

Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 1-2, 4-9, 14, 24-29, 34-37, 41 and 47-49 stand rejected under 35 U.S.C. §112 second paragraph as allegedly indefinite. Office Action, page 5, item 15. This rejection is respectfully traversed as described below.

Claims 1-2, 4-9, 14, 24-29, 34-37, 41 and 47-49 are asserted to be unclear as to the intent of the reducing step. Office Action, page 6, item 15(a). Applicants respond that the

understand that reduction of the introduced cysteine residue promotes dimerization with like moieties.

Claims 1-2, 4-9, 14, 47-48 are rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite because it is unclear how the reduced antibody of claim 1, part (iv) could be contacted with an antibody to produce a heterodimer, as recited in claim 1, part (v). Office Action, page 6, item 15(b). Claim 1, part (v) is amended to recite a second antibody that contains a thiol reactive group other than a cysteine group introduced therein. Claims 2, 4-9, 14, and 47 ultimately depend from claim 1 and thus also include this limitation. Claim 48 depends from claim 24, recites in part (v) use of a second antibody, wherein a thiol-reactive group has been introduced into the second antibody.

Claim 37 is rejected under 35 U.S.C. § 112, second paragraph as allegedly unclear as to how a heterodimer which binds to two distinct antigens can be produced when only one antibody with one specificity is used to prepare the dimer. Office Action, page 6, item 15(c). This rejection is moot because claim 37 is canceled.

Claims 28 and 41 are rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for depending on non-elected claims. Office Action, page 6, item 15(d). Claims 28 and 41 are amended to properly depend from elected claim 24.

Claims 1-2, 4-9, 14, 24-29, 34-37, 41, 47-49 are rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite in recitation of an "antibody molecule heavy chain that has binding specificity." Specifically, the examiner contends that it is unclear whether the binding specificity is a property of the heavy chain alone or the heavy chain when paired with a corresponding light chain. Office Action, page 6, item 15(e). Claims 1 and 24 are amended to recite a binding specificity when said heavy chain is paired with a corresponding light chain

Based on the foregoing, claims 1-2, 4-9, 14, 24-29, 34-37, 41 and 47-49 are believed to fully comply with the requirements of 35 U.S.C. § 112, second paragraph. Therefore, applicants respectfully request withdrawal of the rejection of claims under § 112, second paragraph.

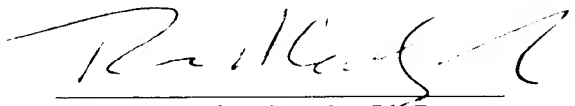
Conclusion

All rejections having been addressed, it is respectfully submitted that the present

personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

PILLSBURY WINTHROP LLP



Thomas A. Cawley, Jr., Ph.D.
Registration No. 40,944

1600 Tysons Blvd
McLean, Virginia 22102
(703) 905-2144 (Direct Dial)
(703) 905-2500 (Facsimile)

Date: March 28, 2003

APPENDIX

1. (Three Times Amended) A method for producing an antibody heterodimer [composed of two different antibody molecules having binding specificity to two distinct antigens, wherein the method comprises] comprising:

(i) obtaining or constructing a DNA molecule that encodes an antibody molecule heavy chain that has binding specificity to a first antigen when said heavy chain is paired with a corresponding light chain, and introducing at least one cysteine codon into said antibody molecule heavy chain via recombinant DNA mutagenesis, wherein the location of [the] said cysteine does not interfere with the antigen binding properties of [the] said heterodimer;

(ii) expressing said DNA molecule in a suitable host cell, or expression system, together with a DNA molecule that encodes an antibody molecule light chain [of] having the same specificity as the heavy chain, to produce [an] a first antibody molecule containing said introduced cysteine residue;

(iii) purifying said first antibody molecule from said host cell or expression system;

(iv) contacting said purified first antibody molecule with an amount of a suitable reducing agent sufficient to partially reduce the intra or inter molecular disulfide bonds of said first antibody molecule [and] to thereby enhance [the formation of antibody dimers] dimerization of said first antibody molecule with a second antibody molecule; and

(v) contacting said purified first antibody molecule with [another] a second antibody molecule, wherein said second antibody has a binding specificity to a second antigen, [having antigen specificity other than the antigen specificity of the antibody molecule purified in step (iii)] wherein said second antibody contains a thiol reactive group [and which does not have] other than a cysteine group introduced therein; and allowing sufficient time for [the] dimerization [reaction] to proceed; to thereby [producing] produce [said] an antibody heterodimer comprised of said first antibody molecule and said second antibody molecule, wherein each antibody molecule retains its binding specificity following dimerization.

24. (Three Times Amended) A method for producing an antibody heterodimer [composed of two different antibody molecules, having binding specificity to two distinct antigens, wherein the method comprises] comprising:

(i) obtaining or constructing a DNA molecule that encodes an antibody molecule heavy chain that has binding specificity to a first antigen when said heavy chain is paired with a corresponding light chain, and introducing at least one cysteine codon into said antibody molecule heavy chain via recombinant DNA mutagenesis, wherein the location of [the] said cysteine does not interfere with the antigen binding properties of [the] said heterodimer;

(ii) expressing said DNA molecule in a suitable host cell, or expression system, together with a DNA molecule that encodes an antibody molecule light chain [of] having the same specificity as the heavy chain, to produce [an] a first antibody molecule containing said introduced cysteine residue;

(iii) purifying said first antibody molecule from said host cell or expression system;

(iv) contacting said purified first antibody molecule with an amount of a suitable reducing agent sufficient to partially reduce the intra or inter molecular disulfide bonds of said first antibody molecule [and] to thereby enhance [the formation of antibody dimers] dimerization of said first antibody molecule with a second antibody molecule; and

(v) [adding] introducing a thiol reactive group on [another] a second antibody molecule, wherein said second antibody has a binding specificity to a second antigen, [having antigen specificity other than the antigen specificity of the antibody molecule purified in step (iii) and which] and wherein said second antibody does not have a cysteine group introduced therein; and allowing sufficient time for [the] dimerization [reaction] to proceed; to thereby [producing] produce [said] an antibody heterodimer comprised of said first antibody molecule and said second antibody molecule, wherein each antibody molecule retains its binding specificity following dimerization.

28. (Twice Amended) An IgG/IgG dimer produced by the method of Claim [22]

41. (Twice Amended) A pharmaceutical composition comprising an IgG/IgG dimer according to Claim [22] 24, and a pharmaceutically acceptable carrier.

45. (Twice Amended) A method for producing an IgG/IgG [dimer] heterodimer comprising [genetically engineering] preparing a first IgG MAb having binding specificity to a first antigen, introducing a cysteine residue in said first IgG MAb [molecule placed in] at a position which does not interfere with the antigen binding properties of said heterodimer, and which inhibits or prevents formation of an intramolecular disulfide bridge between sister heavy chains on the same antibody molecule, and exposing said first IgG MAb [Mab] to a second IgG [Mab] MAb having a binding specificity to a second antigen, whereby said first and second IgG MAbs dimerize to produce said IgG/IgG [dimer] heterodimer comprised of said first IgG MAb and said second IgG MAb, wherein each IgG retains its binding specificity following dimerization.